Hypoglycemia as a risk factor for dementia development in diabetic patients: a systematic review

La hipoglucemia como factor de riesgo para el desarrollo de demencia en pacientes diabéticos: revisión sistemática

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Resumen

Recurrent hypoglycemia has been identified as a significant risk factor for the development of dementia in patients with diabetes mellitus, both Type 1 and Type 2. Several studies suggest that hypoglycemic episodes, especially severe ones, can trigger structural alterations in the brain, such as brain volume loss and cortical atrophy, which contribute to cognitive decline. Hypoglycemia can induce direct neuronal damage, affecting key brain areas such as the hippocampus, and can also lead to cerebral hypoperfusion. Objective: This study aims to evaluate the relationship between hypoglycemic episodes and the development of dementia in diabetic patients through a systematic review of the available scientific literature. Methodology: A descriptive systematic literature review was conducted following the PRISMA guidelines focusing on qualitative analysis of cohort studies that explore hypoglycemia as a risk factor for dementia in diabetic patients. Results: The results indicate that in patients with Type 1 diabetes, repeated exposure to hypoglycemic episodes can double the risk of developing dementia in old age. In Type 2 diabetes, the incidence of dementia increases by 25.4% in those with a history of hypoglycemia. The frequency and severity of hypoglycemic episodes are directly related to an increased risk of cognitive impairment, particularly in older adults. These findings highlight the importance of adequate glucose management in diabetic patients to minimize hypoglycemic episodes and, consequently, prevent the development of dementia, especially in individuals with comorbidities or early signs of cognitive decline.

Keywords: hypoglycemia, dementia, cognitive risk, diabetes mellitus

Resumen

La hipoglucemia recurrente se ha identificado como un factor de riesgo significativo para el desarrollo de demencia en pacientes con diabetes mellitus, tanto tipo 1 como tipo 2. Diversos estudios sugieren que los episodios hipoglucémicos, especialmente los graves, pueden desencadenar alteraciones estructurales en el cerebro, como la pérdida de volumen cerebral y atrofia cortical, lo que favorece el deterioro cognitivo. La hipoglucemia puede inducir daño neuronal directo, afectando áreas cerebrales clave como el hipocampo, y también generar hipoperfusión cerebral. Objetivo: evaluar la relación entre los episodios de hipoglucemia y el desarrollo de demencia en pacientes con diabetes a través de una revisión sistemática de la literatura científica disponible. Metodología: Se llevó a cabo una revisión sistemática de la literatura de carácter descriptivo, para realizar este proceso se siguió la declaración de PRISMA. Resultados: Los estudios demostraron que en pacientes con diabetes tipo 1, la exposición repetida a episodios hipoglucémicos puede duplicar el riesgo de desarrollar demencia en la vejez. En diabetes tipo 2, la incidencia de demencia aumenta en un 25.4% en aquellos con antecedentes de hipoglucemia. La frecuencia y gravedad de los episodios hipoglucémicos están directamente relacionadas con un mayor riesgo de deterioro cognitivo, especialmente en adultos mayores. Estos hallazgos subrayan la importancia de un manejo adecuado de la glucosa en pacientes con diabetes para minimizar los episodios hipoglucémicos y, de este modo, prevenir el desarrollo de demencia, particularmente en aquellos con comorbilidades o con signos incipientes de deterioro cognitivo.

Palabras clave: hipoglucemia, demencia, riesgo cognitivo, diabetes mellitus

Introduction

Diabetes mellitus (DM) stands out as one of the most prevalent chronic conditions globally, while simultaneously being the most frequent endocrine disease. It is characterized for persistently elevated blood sugar levels and, depending on the type of diabetes, insulin resistance or insulin depletion. This condition compromises over 500 million people worldwide and is expected to grow even further in the coming years, rendering it a true public health concern. Moreover, the health expenditures in 2021 attributed to DM and its associated complications scaled up to US$966 billion globally, forecast to reach more than $1054 billion by 20451. Apart from the already known micro and macrovascular complications—such as retinopathy, neuropathy, nephropathy, and cardiovascular disease— there has been increasing recognition of its impact in neurological health. Several studies suggests that DM is associated with heightened risk of cognitive impairment and dementia, which adds another layer of complexity in the management of DM[2,3].

Although the link between DM and neurological disorders is well documented, there has been a growing interest on the role of hypoglycemia in this process. Hypoglycemia is the most frequent metabolic emergency in diabetic patients undergoing insulin therapy, albeit it is less frequent and severe in patients with type 2 DM (DM2)[4]. Hypoglycemia is defined as glycemia levels under the reference range, which is typically (<70 md/dL). However, the role of hypoglycemia in the development of dementia remains a topic of interest. Newer evidence has shown that the acute metabolic stress linked with this complication can cause neuroinflammation and neuronal dysfunction, especially in vulnerable regions like the hippocampus. Therefore, repetitive exposure to such episodes could accelerate neurodegenerative mechanisms and contribute to the onset of dementia[5,6].

The direct link between hypoglycemia and dementia is yet to be elucidated. Some authors have stated positive, negative, and mixed outcomes, which highlights the uncertainty regarding this topic. The need for a systematic review is evident, given the need to clarify the link between these two entities, in order to provide solid grounds for clinicians and their decision-making regarding the management of DM and the proper resolution of hypoglycemic episodes. The aim of this review is to enhance the understanding of the mechanisms connecting hypoglycemia and dementia to optimize the management of diabetic patients from a more integral perspective, and to make a positive impact in the clinical practice of general practitioners.

Materials and methods

This study adopts a systematic review design following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, focusing on qualitative analysis of cohort studies that explore hypoglycemia as a risk factor for dementia in diabetic patients. The research question aligns with the PEO framework (Population: diabetic patients; Exposure: hypoglycemic episodes; Outcomes: dementia risk). Inclusion criteria prioritize studies published between 2016–2025 in Spanish, English, Portuguese, or Russian, with open-access availability and statistically significant findings. The excluded materials were systematic reviews, meta-analyses, theses, and studies which lacked relevant data or translations.

Data was sourced from databases like Scopus, PubMed, and ScienceDirect. Keyword combinations (e.g., "hipoglucemia AND demencia") and Boolean operators refined the search leading to obtain the following: (("hipoglucemia") AND ("demencia")) OR ("factor de riesgo")), Figure 1. Tools like Rayyan and Zotero streamlined article screening and eliminated duplicates. Study quality was assessed using the NHLBI scale for observational cohorts, while the Cochrane Collaboration's ROB-1 tool evaluated bias risk, excluding studies with non-significant results or insufficient data. This dual-layer scrutiny ensured robust, bias-minimized evidence synthesis.

Results and Discussion

DM represents far more than just elevated blood glucose; it's a complex metabolic disorder where the body's insulin system fails, either through inadequate production or ineffective use of this crucial hormone. This dysfunction creates a dangerous seesaw effect: while chronic high glucose slowly damages organs, the sudden plunges into hypoglycemia pose immediate neurological threats, triggering a myriad of symptoms from sweating and confusion to seizures and coma[7]. On the other end of the spectrum lies dementia, where insidious cognitive impairment may manifest in many ways; most commonly in this population as Alzheimer's disease or vascular dementia. Although the role of DM is very well-known in the development of dementia, the impact of hypoglycemia remains a possible alternative to neurological deterioration leading to cognitive impairment.

The relationship between hypoglycemia and dementia is, presumably, mediated by three key mechanisms. First, recurrent hypoglycemia induces neuronal damage through glucose deprivation and oxidative stress, particularly in the hippocampus. Second, diabetes-related microvascular dysfunction exacerbates cerebral hypoperfusion, increasing vulnerability to vascular dementia. Third, severe hypoglycemic episodes may accelerate Alzheimer's pathology by promoting amyloid-beta accumulation[2,8]. Epidemiological studies indicate diabetics with prior episodes of hypoglycemia have 1.5–2 times

Figure 1. Flow Chart, PRISMA 2020.

N	Author(s)	Population	Comorbidities	Adjusted Variables	Risk modification	Reference
1	Whitmer R et al. (2022)	2,821 (T1DM)	HTN, hyperlipidemia, stroke, depression	Race, ethnicity	HR: 1.66 (95% CI: 1.09-2.53)	(10)
2	Zheng B et al. (2021)	19,510 (T2DM)	Obesity, HTN, smoking, COPD	Ethnicity, HbA1c levels	HR: 1.08 (95% CI: 1.07-1.09)	(20)
3	Kim Yong G et al. (2019)	5,966 (T2DM)	Stroke, IHD, MI	Sex, economic status, antidiabetic meds	HR: 1.17-1.30 (episode-dependent)	(25)
4	Moran C et al. (2023)	253,211 (T2DM)	Micro/macrovascular complications	Sex, race, ethnicity	HR: 1.74 (95% CI: 1.15-1.51)	(18)
5	Alsharif A et al. (2023)	133,664 (T1DM/T2DM)	HTN, microvascular complications, obesity	Diabetes duration, dementia type	HR: 2.25 (95% CI: 2.22-2.32)	(26)
6	Han E et al. (2022)	14,443 (T2DM)	HTN, cerebrovascular disease, IHD	BMI, additional meds	HR: 1.80 (95% CI: 1.66-1.94)	(27)
7	Alkabbani W et al. (2022)	13,970 (T2DM)	Diabetes severity indicators	Sex, diabetes duration, SES, hospitalizations	HR: 1.83 (95% CI: 1.31-2.57)	(14)
8	Hemalkumar B et al. (2017)	53,055 (T2DM)	BMI, alcohol, smoking	Race, hypoglycemic agents	HR: 1.27 (95% CI: 1.06-1.51)	(28)
9	Lee A et al. (2019)	15,792 (T2DM)	Not specified	Race, BMI, education, antidiabetics	OR: 2.34 (95% CI: 1.04)	(17)
10	Sang Chin O et al. (2016)	4,540 (T2DM)	Previous diseases	BMI, diabetes duration	OR: 2.69 (95% CI: 1.080)	(29)
11	Mattishent K et al. (2019)	1,098 (T2DM)	Not specified	Sex, diabetes duration	OR: 2.24% (95% CI: 1.14-1.26)	(24)
12	Chung-Yi Li et al. (2022)	35,720 (T2DM)	HTN, COPD, obesity, depression	Gender, urbanization, income	HR: 1.14-1.31	(19)
13	Chi-Ho Lee et al. (2020)	85,514 (T2DM)	Macro/microvascular complications	Hypoglycemia risk factors	2.3% vs 1.2% (p<0.001)	(30)

higher dementia risk, suggesting a bidirectional relationship as cognitive impairment worsens hypoglycemia awareness, further increasing dementia susceptibility. These findings underscore the need for glucose management strategies that mitigate long-term neurological risks[9].

The comprehensive analysis of current evidence reveals a robust association between hypoglycemic episodes and increased dementia risk across both major diabetes types, with distinct pathophysiological and epidemiological patterns emerging from the reviewed studies. For simplicity purposes, the findings were segmented into two major groups, for DM1 and DM2.

The impact of hypoglycemia appears particularly pronounced in DM1 populations. Whitmer et al.'s10 landmark study on 2,821 patients demonstrated that three-quarters of subjects developed dementia following hypoglycemic events, establishing hypoglycemia as a major modifiable risk factor. These results were corroborated by Lee et al.11, whose work revealed DM1 patients with hypoglycemia exposure faced double the dementia risk compared to their non-exposed counterparts (OR: 2.0, 95% CI: 1.5-2.7). Notably, both research teams identified insulin therapy as a potential mediator of this relationship, with Lee's team specifically highlighting that intensive insulin regimens–while beneficial for glycemic control–may paradoxically elevate dementia risk through increased hypoglycemia frequency. This emphasizes the need for more individualized insulin regimens[11].

On the other hand, available DM2 data presents a more complex but equally concerning picture. Kim et al.'s12 massive cohort study (n=458,000) documented several critical findings. Firstly, a 25.4% increased dementia risk following hypoglycemia; furthermore, 28,627 incident dementia cases within just six years (6.3% incidence). Equally relevant, a clear temporal relationship was established with their hazard ratios showing a steady uptrend the longer the follow-up (HR:1.10 at 6 years, projected to rise further). Similarly, Chin et al.13 (n=6,000) revealed even more striking associations by reporting a hazard ratio of 2.68 translating to 168% elevated risk, and an incidence rate of 7.5 cases per 1000 person-years, nearly doubling their non-hypoglycemic counterpart. On a separate thought, findings from Asian population are particularly relevant given the known variations of DM and its complications given the ethnicity. Nonetheless, this also makes the reproducibility of such studies in other populations more challenging.

The work of Alkabbani et al.14, and other Canadian researchers15, has precisely quantified the cumulative nature of this risk, showing that the larger the quantity of episodes, the worse the outcomes. Precisely, a single episode of hypoglycemia was associated with a 15% increased risk of dementia (HR:1.15), scaling up to 21 and 25.4% for two and three or more episodes respectively (HR:1.21 and HR:1.254). Moreover, in-hospital hypoglycemia was associated with an additional 15% risk of dementia in contrast to outpatient-managed events. This gradient was further validated by U.S. cohort data showing dementia risk doubling following severe hypoglycemia after age 4514,15, with particularly strong associations for events occurring in midlife versus later years (adjusted HR: 2.3 vs 1.7).

In light of the above, the link between hypoglycemia and dementia is hardly questionable from a quantitative perspective. However, its biological plausibility is a separate matter. Along these lines, several investigations have tried to elucidate neuropathological pathways to explain the pathophysiological nexus between these two entities. Lee et al. and Han et al.16,17 documented progressive brain volume loss equivalent to 7 years of accelerated aging following episodes of hypoglycemia, particularly affecting the hippocampus and prefrontal cortex. Likewise, Moran et al.18 demonstrated hypoperfusion-mediated neuronal injury, while Taiwanese researchers19 highlighted microvascular damage from comorbid hypertension. Nevertheless, no adjustment for confounders were performed, so this evidence could be considered low-quality. Finally, Zheng et al.20 identified oxidative stress markers and amyloid precursor protein dysregulation in hypoglycemia-exposed patients, both of which are heavily associated with Alzheimer's disease.

Comorbidities are extremely frequent with DM, and as a result, their impact on the progression of dementia is another topic of high interest. Currently available evidence has shown that the combination of DM and hypoglycemia with other conditions tends to have a multiplicative behavior when analyzing attributable risk. For instance, up to 60-70% of patients with dementia and this combination may also have obesity and/or hypertension15,19. In addition, DM, hypertension and obesity are all independently correlated with chronic inflammation and neuroinflammation[21,22], blood-brain barrier dysfunction20, and insulin resistance exacerbation23, mechanisms that have been all linked to dementia. However, to date there is no available evidence showing the exact independent impact of each comorbidity taking as a primary outcome the incidence of dementia, at least considering hypoglycemia as the main variable.

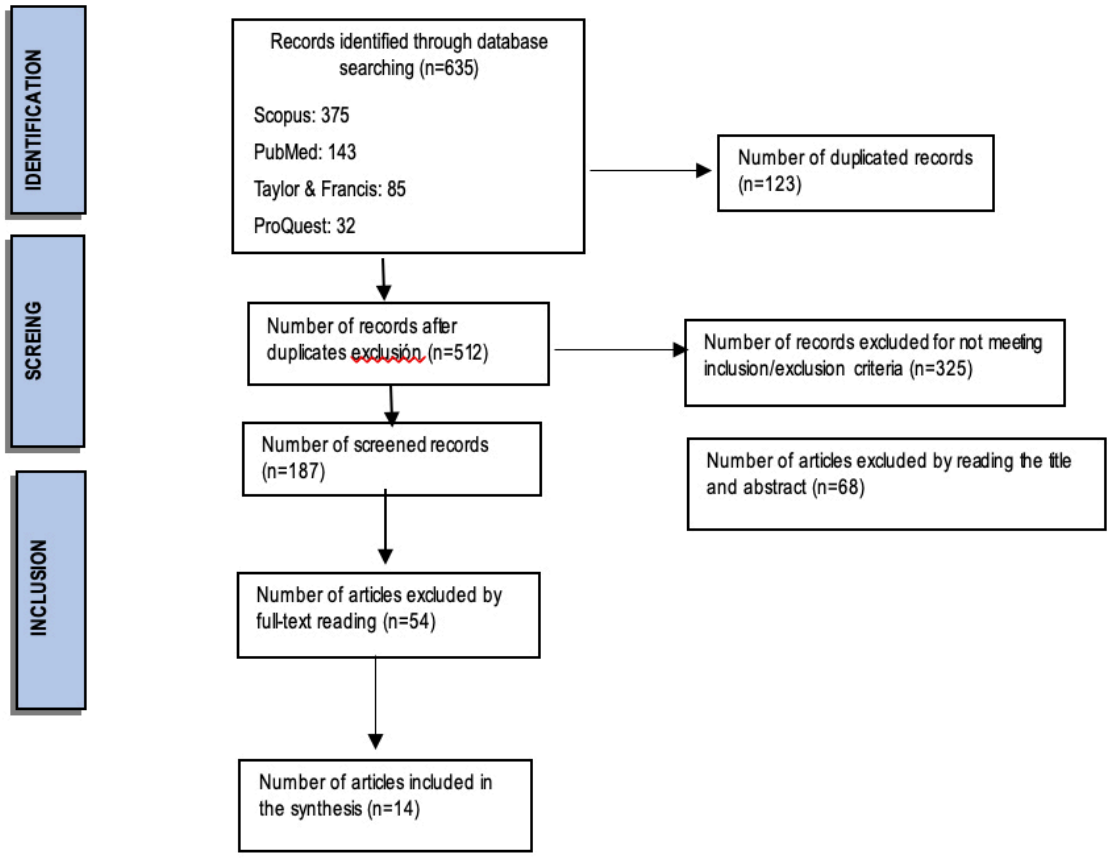
It is well-known that age plays a key role in dementia onset. As a consequence, Matteishent et al.'s[24] carried out a geriatric-focused research that reported a peak in susceptibility after 75 years of age. On the other hand, socioeconomic status provided no protection whatsoever, indicating universal risk. It was also reported that the loss of counterregulatory capacity increased the risk of dementia, especially after 40% reduction in glucagon response. Lastly, polypharmacy was heavily prevalent in the studied group and particularly the interactions between antihypertensive and antidiabetic drugs seemed to increase the risk of hypoglycemia and, thus, the risk of dementia.

Collectively, these findings highlight the importance of cognitive screening in hypoglycemia-prone patients and

the need for age-adjusted glycemic targets beyond the coexistence of frailty. Moreover, proper comorbidity management is vital to decrease the risk of dementia while also aiming to use the least amount of drugs to avoid deleterious interactions. In addition, continuous glucose monitoring in high-risk groups alongside proper education could potentially optimize glycemic management, although there is lacking evidence regarding this topic. For a more concise picture of the analyzed studies refer to Table 1.

While the evidence is compelling, several constraints merit consideration. Firstly, there is high heterogeneity in the diagnostic criteria for dementia across the analyzed evidence, and the follow-up duration of most studies range between 6 to 15 years. More importantly, the hypoglycemia documentation method significantly varies across studies, some using only clinical criteria, making results hard to reproduce and compare. Furthermore, the residual confounding factors from unmeasured vascular risk factors and genetic predispositions generates several questions that would need to be addressed in future research. At last, there is limited data regarding racial variations and even less data targeting specific dementia subtypes. Although several questions remain unanswered, it is expected that the above analysis and recommendations lead future researchers towards methodological optimizations to provide better insights on this topic.

Figure 1. Flow Chart, PRISMA 2020.



Conclusions

This systematic review confirms that hypoglycemia represents a significant risk factor for the development of dementia in both DM1 and DM2 patients. Evidence demonstrates a dose-dependent relationship, where patients experiencing ≥3 hypoglycemic episodes face substantially higher cognitive decline risk (25.4% increased risk). The neurological impact occurs through multiple pathways: acute glucose deprivation causing hippocampal and prefrontal cortex damage, progressive gray matter atrophy, cerebral hypoperfusion, oxidative stress-induced neuroinflammation. These mechanisms may be exacerbated by comorbidities like hypertension and obesity, which accelerate neurodegeneration. Crucially, hypoglycemia emerges not merely as a disease marker but as an active contributor to dementia pathogenesis, necessitating targeted prevention strategies.

Clinical management should prioritize individualized glycemic targets (HbA1c 6-7.5% for elderly patients) and hypoglycemia prevention through continuous glucose monitoring and high-risk medication avoidance. Patient and caregiver education programs must emphasize early symptom recognition, while multidisciplinary approaches should address comorbid conditions. Future research directions include: mechanistic studies elucidating causal pathways, clinical trials evaluating neuroprotective interventions, and longitudinal analyses of prevention strategies. Technological integration (e.g., AI-driven glucose prediction) and comparative effectiveness studies of antidiabetic regimens will be critical for developing evidence-based guidelines that balance metabolic and cognitive outcomes.

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